DATA EVALUATION RECORD

DICAMBA BAPMA SALT

STUDY TYPE: 28-DAY INHALATION TOXICITY – RAT
(OCSPP 870.3465)

MRID 49441803

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
Knoxville, Tennessee 37922

Task Order No. 6-118

Primary Reviewer:	
Thomas C. Marshall, Ph.D., DABT	Signature: _____
	Date: _____
Secondary Reviewers:	
H. Tim Borges, Ph.D., DABT	Signature: _____
	Date: _____
Robert Ross, M.S., Program Manager	Signature: _____
	Date: _____
Quality Assurance:	
Angela M. Edmonds, B.S.	Signature: _____
	Date: _____

Disclaimer
This review may have been altered subsequent to the contractor's signatures above.

Summitec Corp. for the U.S. Environmental Protection Agency under Contract No.EP-W-11-014

EPA Reviewer: William Irwin, PhD, DABT **Signature:** _____
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** _____
EPA Secondary Reviewer: Ayaad Assaad, DVM, PhD **Signature:** _____
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** _____

Template version 09/11

TXR#: None

DATA EVALUATION RECORD

STUDY TYPE: 28-Day Inhalation Toxicity - Rat OCSPP 870.3465.

PC CODE: 100094 **DP BARCODE:** None

TEST MATERIAL (PURITY): Dicamba BAPMA Salt (84.7% w/w, equiv. to 69.5% Dicamba acid)

SYNONYMS: BAS 183 22H.

CITATION: Lan Ma-Hock, et al. Dicamba BAPMA Salt: 28-day inhalation toxicity study in Wistar rats, dust exposure. BASF SE, Experimental Toxicology and Ecology, Germany. Project No.: 4010519/131076, August 15, 2014. MRID 49441803. Unpublished.

SPONSOR: BASF SE (Germany).

EXECUTIVE SUMMARY:

In a nose-only inhalation toxicity study (MRID 49441803), four groups of Crl:WI(Han) rats (10/sex/group; ~10 weeks of age) were administered Dicamba BAPMA Salt [84.7%, equivalent to 69.5% Dicamba acid (Batch No. 1781-6)] as a dust aerosol at target exposure concentrations of 0, 0.0014, 0.0072, or 0.036 mg/L (respective actual concentrations of 0, 0.0015, 0.0070, and 0.0352 mg/L) for 28 days.

There were no mortalities or clinical signs observed at any exposure concentration. No substance-related adverse findings were observed on body weight, ophthalmology examinations, food consumption, or clinical pathology parameters in blood. Plasma concentrations of Dicamba acid after 22 days of exposure increased with exposure concentration, but not proportionally to the 5-fold increase in exposure between the mid- and high-exposure concentrations. The respective mean values of female animals were higher than those of the males. Microscopic examination of tissues showed that the test substance was a respiratory tract irritant with adverse effects on the nasal cavity, larynx, trachea, lungs, and the lung-associated lymph nodes. **Nasal cavity**: In Level I, focal degeneration/regeneration of the respiratory and/or transitional epithelium was observed in 1 male and 1 female from the mid exposure group (minimal severity), and in 8 males and 5 females from the high exposure group (minimal to slight). Two males and two females at the high concentration showed minimal focal squamous cell metaplasia of the respiratory epithelium in the septum. In Level II, one female at the high concentration showed an ulcer in the epithelium of the septum. **Larynx**: Ulcers in epithelial tissues were

observed in males at incidences of 2/10, 5/10, and 8/10, respectively, in the low-, mid-, and – high-exposure groups. Minimal focal inflammation was observed in Level I or Level II in 3 males at the low concentration, 1 male and 1 female at the mid concentration, and in 1 male and 3 females at the high concentration. Single or multi-focal hyperplasias were observed in Level I and/or Level II in 5 males and 4 females at the low concentration, 8 males and 7 females at the mid concentration, and in 7 males and 7 females at the high concentration. **Trachea**: Minimal or slight focal degeneration/regeneration of the respiratory epithelium was observed in 2 males at the mid concentration, and in 5 males and 1 female at the high concentration. **Lung**: Minimal to slight inflammation was observed in bronchi and/or alveoli in most to all of the males and females at the mid- and high-concentration. Minimal multifocal bronchiolo-alveolar hyperplasia was observed in 2 males at the high concentration and in 1 female at the mid concentration. Minimal hypertrophy of single terminal bronchi was observed in 6 males and 3 females at the high concentration. The incidence of minimal or slight multifocal alveolar histiocytosis increased in males from all three exposed groups and in females from the mid- and high-concentration groups. The incidence of minimal or slight alveolar macrophage aggregates was increased in males at the mid- and high-concentration and in females from all three exposed groups. Tracheobronchial and mediastinal lymph nodes: Minimal to slight lympho-reticulocellular hyperplasia in one or both of these lymph nodes was observed in males at the mid- and high-exposure concentrations and in females at all three concentrations. Macrophage aggregates were observed in both sexes at the mid- and high-exposure concentrations.

The LOAEL in Wistar rats was 0.0014 mg/L based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasias in the larynx. A NOAEL was not identified.

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for 4-week inhalation toxicity study in rats (OCSPP 870.3465).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Dicamba BAPMA Salt

Description:	White to yellowish solid
Lot/batch #:	1781-6
Purity:	84.7% w/w, equiv. to 69.5% Dicamba acid
CAS # of TGAI:	Not provided or available at ChemID
Structure:	Not provided or available at ChemID

2. Vehicle: Charcoal and HEPA filtered air.

3. Test animals:

Species:	Rat	
Strain:	Crl:WI(Han)	
Age/weight at study initiation:	~10 weeks/ Males = 231-278 g; Females mean range = 173-201 g	
Source:	Charles River Laboratories, Inc., Sulzfeld, Germany	
Housing:	Five per polysulfonate cage with dust-free wooden bedding	
Diet:	Kliba maintenance diet, Provimi Kliba SA, *ad libitum* except during exposure	
Water:	Tap water, *ad libitum* except during exposure	
Environmental conditions:	**Temperature:**	20-24 °C; 20.7-22.4 °C during exposure
	Humidity:	30-70%; 37.7-52.8% during exposure
	Air changes:	15/hour; 67/hour during exposure
	Photoperiod:	12 hours light/dark
Acclimation period:	About 14 days; 3 days to exposure system	

B. STUDY DESIGN:

1. **In-life dates:** Start: January 8, 2014; End: February 5, 2014

2. **Animal assignment and treatment:** Rats were randomly assigned by computer to experimental groups based upon body weights not varying by more than ±20% of the mean (Table 1). Concentrations were selected for the 28-day study by the Sponsor. The high concentration of 0.036 mg/L corresponds to about 0.025 mg/L Dicamba acid, the mid concentration (0.0072 mg/L) to approximately 0.0005 mg/L and the low concentration (0.0014 mg/L) to about 0.001 mg/L.

TABLE 1. Study Design				
Experimental parameter	Exposure concentrations (mg/L)			
	Group 0 0	Group 1 0.0014	Group 2 0.0072	Group 3 0.036
Number of Rats				
Total no. of animals assigned	20 (10/sex)	20 (10/sex)	20 (10/sex)	20 (10/sex)
Sacrifice and necropsy	20 (10/sex)	20 (10/sex)	20 (10/sex)	20 (10/sex)
Behavioral testing (FOB, Motor Activity)	Not done in this study			
Blood cholinesterase determination	Not done in this study			
Measured Concentration				
Achieved aerosol conc. (mg/L ± s.d.)	NA	0.0015 ± 0.0002[a]	0.0070 ± 0.0011[a]	0.0352 ± 0.0051[a]

Data obtained from pages 23 & 48 (MRID 49441803)
[a] MMADs were within the Guideline recommended range of 1-3 µm.

3. **Generation of the test atmosphere / chamber description:** The test material was desagglomerated with a household mixer (Braun, type MX32), sieved in a screening machine (250 µm mesh; Prufsieb JEL 200), and the resulting powder mixed with 1% Aerosil 200 to increase its flowability. Chamber atmospheres were generated using solid particle brush generators (BASF SE, Germany) coupled with mixing chambers, cyclonic separators (BASF SE, Germany), and a distribution system that delivered controlled amounts of dust aerosol and filtered compressed air to the inlet of each 90 L nose-only exposure chamber (INA 60, BASF SE, Germany). The exposure chambers (one for each exposure level) were fitted with air flow meters, pressure gauges, and other devices to measure temperature, humidity, and test article concentration. The animals were acclimatized to the restraining devices for three days prior to the commencement of exposures.

4. **Test atmosphere concentration:** The exposure concentrations in each exposure chamber were measured real-time using scattered light photometers (Vis-Guard) and gravimetrically three times per day (2/day for the low concentration). Samples were taken from the breathing zone of the animals using pre-weighed filters. Results are in Table 1 and show that the achieved mean test substance concentrations were 107, 97, and 98% of target values for the low, mid, and high exposure concentrations, respectively. Homogeneity of concentrations and any rotation of animals was not addressed. Time to equilibrium was not reported.

5. **Particle size determination:** Particle size for each exposure concentration was determined once weekly during the study using Marple 298 stack samplers (New Star Environmental, Roswell, GA). The mass median aerodynamic diameter (MMAD) and geometric standard deviation (σg) ranges were 1.9-2.1 µm (2.1-3.4), 1.6-2.1 µm (2.0-2.2), and 2.2-2.5 µm (1.9-2.2) for the low-, mid-, and high-concentration groups, respectively.

6. **Statistics:** Each test substance-exposed group was compared to the control group by sex. The overall minimum level of significance for intergroup differences was $p \leq 0.05$ except when noted otherwise. Body weight and body weight change were analyzed using Dunnett's test (two-sided). Nonparametric data (blood parameters) were analyzed using the one-sided Kruskal-Wallis test followed by pairwise comparisons using the Wilcoxon test (two-sided). Absolute and relative organ weights were analyzed using the two-sided Kruskal-Wallis test followed by pairwise comparisons using the Wilcoxon test (two-sided) for the hypothesis of equal medians. The Reviewer considers the statistical testing appropriate.

C. METHODS / OBSERVATIONS:

1. **Mortality and clinical observations:** Animals were observed for abnormal behavior, mortality and morbidity at least twice daily; before, after, and during exposure on exposure days; once on weekends and holidays. Detailed clinical observations were not conducted.

2. **Body weight:** Animals were weighed prior to exposure, on test day 0 (first administration of exposure), and twice weekly thereafter.

3. **Food consumption:** The amount of food consumed was estimated for each animal by cage and was recorded weekly. Feed efficiency was not calculated.

4. **Cholinesterase determination:** Cholinesterase activity was not measured.

5. **Ophthalmoscopic examination:** Eyes of rats from all experimental groups were dilated with a mydriatic agent and examined by an ophthalmoscope prior to the first day of exposure, and eyes of rats from the control and high dose groups were examined at the end of the study.

6. **Plasma concentration of the test substance:** Blood from the retro-orbital sinus was collected from all animals (non-fasted) on day 22 while under isoflurane anesthesia, and the plasma separated and frozen for later analysis of Dicamba acid content using reverse phase HPLC coupled with electrospray ionization mass spectrometry.

7. **Hematology and clinical chemistry:** Blood was collected for hematology and clinical chemistry from all surviving animals at the end of the experimental period; the animals were fasted overnight prior to blood collection. Blood was collected from the retro-orbital sinus while the rats were under isoflurane anesthesia. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

b. Clinical chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
X	**ENZYMES** (more than 2 hepatic enzymes eg., *)	X	Total bilirubin
X	Alkaline phosphatase*	X	Total serum protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		Bile acids
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		
	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

8. **Urinalysis:** Not conducted.

9. **Sacrifice and pathology:** At study termination, all surviving rats were euthanized by exsanguination while under pentobarbital anesthesia and necropsied. Any gross lesions were recorded. Tissues from animals in all exposure groups were processed for microscopic evaluation. Microscopic examination was conducted on all tissues from the control and high exposure groups, while teeth, trachea, pharynx, larynx, liver, nasal cavities, lymph nodes, and lung were examined for all animals. The following CHECKED (X) tissues were collected. The (XX) organs were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+	X	GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	X	UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	XX	Thyroid*
XX	Liver*+	XX	Testes*+	X	OTHER
	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*		Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin
X	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+	X	Harderian gland
XX	Lung*	X	Mammary gland*	X	Teeth
X	Nasal cavity* (4 levels)				
X	Pharynx*				
X	Larynx*				

* Recommended for subchronic rodent studies based on Guideline 870.3465
+ Organ weights required

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs and Mortality:** There were no mortalities or clinical signs observed at any exposure concentration.

B. BODY WEIGHT AND BODY WEIGHT GAIN: Selected body weight data are presented in Table 2. No significant effect was observed on body weight or body weight change of either sex during the study. Cumulative weight gain of males at the high concentration was statistically lower (-40%; $p \leq 0.05$) for the 0-28 day interval. Cumulative weight gain in females at the high concentration was lower over the course of the study, though by variable amounts and not statistically significant.

TABLE 2. Body weight and body weight gain

Observation	Exposure concentration (mg/L)			
	0	0.0014	0.0072	0.036
Body weight-males (g ± s.d.)				
Day 0	259 ± 11	259 ± 19	256 ± 10	257 ± 13
Day 6	269 ± 11	267 ± 22	266 ± 13	265 ± 16
Day 13	277 ± 13	277 ± 25	274 ± 16	277 ± 19
Day 27	296 ± 14	294 ± 26	294 ± 17	300 ± 23
Body weight-females (g ± s.d.)				
Day 0	183 ± 8	181 ± 5	183 ± 8	184 ± 9
Day 5	189 ± 9	183 ± 9	186 ± 10	187 ± 10
Day 12	192 ± 10	191 ± 7	195 ± 9	192 ± 11
Day 27	196 ± 12	194 ± 10	200 ± 10	195 ± 12
Body weight gain-males (g)				
Days 0-6	12	10(-17)	10(-17)	8(-33)
Days 0-13	20	20(0)	18(-10)	20(0)
Days 0-27	39	37(-5)	38(-4)	43(+10)
Body weight gain-females (g)				
Days 0-5	6	2(-67)	3(-50)	3(-50)
Days 0-12	9	10(+11)	12(+33)	8(-11)
Days 0-27	13	13(0)	17(+31)	11(-15)

Data obtained from pages 74-75 (MRID 49441803).
Values in ( ) are % difference from controls calculated by reviewer.

C. **FOOD CONSUMPTION**: No effect was observed on food consumption.

D. **BLOOD ANALYSES:**

1. **Hematology:** Mean neutrophil cell counts were statistically higher relative to controls in males from the mid- and high-concentration groups (1.12 and 1.20 giga/L, respectively, vs. 0.83 giga/L in controls). The means were above the historical control range and considered treatment-related.

2. **Clinical chemistry:** No statistically significant or treatment-related findings were observed in either sex in the clinical chemistry data.

3. **Plasma concentration of the test substance:** Table 3 shows the plasma concentrations of Dicamba acid after 22 days of exposure. The plasma concentration increased with exposure concentration, but not proportionally to the 5-fold increase in exposure between the mid- and high-exposure concentrations. The respective mean values of female animals were higher than those of the males.

TABLE 3. Plasma concentrations of Dicamba acid following exposure to Dicamba BAPMA Salt.

Target concentration Dicamba BAPMA Salt (mg/m³)	Corresponding to Dicamba acid (mg/m³)	Mean plasma concentration of Dicamba acid (ng/mL)	
		Male (n = 10)	Female (n = 10)
1.4	1	43.2	84.8
7.2	5	246.0	431.4
36.0	25	593.8	831.0

Data obtained from pages 52 (MRID 49441803).

E. OPHTHALMOSCOPIC EXAMINATION: No treatment-related lesions were observed during the ophthalmoscopic examinations.

F. SACRIFICE AND PATHOLOGY:

1. **Gross pathology:** No treatment-related macroscopic changes were observed in any tissues.

2. **Organ weight:** No statistically significant or treatment-related findings were observed in either sex in the organ weight data.

3. **Microscopic pathology:** The incidences of lesions in the nasal cavity (Level 1) are shown in Table 4. No lesions were observed in Level 1 in controls or the low exposure groups, but a marked increase in the incidences of all lesions was observed in both sexes of the high concentration group. Focal degeneration/regeneration of the respiratory and/or transitional epithelium was observed in 1/10 males and 1/10 females in the mid exposure group (minimal severity), and in 8/10 males and 5/10 females in the high exposure group (minimal to slight). Two males and two females at the high concentration showed a minimal focal squamous cell metaplasia of the respiratory epithelium in the septum. In the nasal cavity (level II), one female at the high concentration showed an ulcer in the epithelium of the septum.

TABLE 4. Incidences of nasal lesions

Nasal cavity, level I	Male animals				Female animals			
Test group (mg/m³)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)
No. of animals	10	10	10	10	10	10	10	10
Degeneration/regeneration	0	0	1	8	0	0	1	5
• Grade 1			1	7				4
• Grade 2				1			1	1
Metaplasia, squamous	0	0	0	2	0	0	0	2
• Grade 1				2				2

Grade 1 = minimal; Grade 2 = slight
Data obtained from page 56 (MRID 49441803).

The incidences of adverse, treatment-related lesions in the larynx are shown in Table 5. Lesions occurred in a concentration-dependent manner in all three groups exposed to the test substance. Ulcers were observed only in males at incidences of 2/10, 5/10, and 8/10, respectively in the low-, mid-, and –high-exposure groups. Ulcers were described in the epithelium lateral to the base of epiglottis (Level I) and/or in the lateral region between the ventral pouch and the arythenoid cartilages (Level II). Minimal focal inflammation was observed in Level I or Level II in 3 males and no females at the low concentration, 1 male

and 1 female at the mid concentration, and in 1 male and 3 females at the high concentration. Single or multi-focal hyperplasias were observed in Level I and/or Level II in 5 males and 4 females at the low concentration, 8 males and 7 females at the mid concentration, and in 7 males and 7 females at the high concentration.

TABLE 5. Incidences of treatment-related larynx lesions

Larynx	Male animals				Female animals			
Test group (mg/m³)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)
No. of animals	10	10	10	10	10	10	10	10
Animals with ulcers	0	2	5	8	0	0	0	0
• Levels I and II			2	6				
• Level I, only		1	1	2				
• Level II, only		1	2					
Animals with inflammation	0	3	1	1	0	0	1	3
• Levels I and II								
• Level I, only		2	1				1	2
• Level II, only		1		1				1
Animals with hyperplasia	0	5	8	7	0	4	7	7
• Levels I and II			1			1	1	
• Level I, only								
• Level II, only		5	7	7		3	6	7

Data obtained from page 56 (MRID 49441803).

In the trachea, minimal or slight focal degeneration/regeneration of the respiratory epithelium was observed in 2 males at the mid concentration, and in 5 males and 1 female at the high concentration.

The incidences of treatment-related lesions in the lung are shown in Table 6. Minimal to slight inflammation was observed in bronchi and/or alveoli in most to all of the males and females at the mid- and high-concentration. The alveolar inflammation was characterized by aggregates of intra-alveolar macrophages, granulocytes, lymphocytes, desquamated epithelial cells and single multinucleated giant cells. The granulomatous inflammation in the bronchi was characterized by loss of epithelium and replacement by macrophage aggregates with other inflammatory cells. Minimal multifocal bronchiolo-alveolar hyperplasia was observed in 2 males at the high concentration and in 1 female at the mid concentration. Minimal hypertrophy of single terminal bronchi was observed in 6 males and 3 females at the high concentration. The incidence of minimal or slight multifocal alveolar histiocytosis (focal accumulation of solitary alveolar macrophages) was increased relative to controls in males from all three exposed groups and in females from the mid- and high-concentration groups, which is an adaptive process and not adverse. The incidence of minimal or slight alveolar macrophage aggregates was increased relative to controls in males at the mid- and high-concentration and in females from all three exposed groups.

TABLE 6. Incidence of treatment-related lung lesions

Lungs	Male animals				Female animals			
Test group (mg/m³)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)
No. of animals	10	10	10	10	10	10	10	10
Inflammation, granulomatous, alveoli	0	0	8	10	0	0	10	8
• Grade 1			8	8			10	7
• Grade 2				2				1
Inflammation, granulomatous, bronchi	0	0	0	3	0	0	0	3
• Grade 1				3				3
Hyperplasia, bronch.-alv.	0	0	0	2	0	0	1	0
• Grade 1				2			1	
Hypertrophy, term. bronch	0	0	0	6	0	0	0	3
• Grade 1				6				3
Histiocytosis, alveolar	1	4	9	10	2	2	4	9
• Grade 1	1	4	9	6	2	2	4	9
• Grade 2				4				
Macrophage aggregates	2	2	9	8	1	4	7	8
• Grade 1	2	2	9	6	1	4	7	7
• Grade 2				2				1
BALT: macrophages/ macrophage aggregates	0	0	0	0	0	0	0	1
• Grade 1								1

Grade 1 = minimal; Grade 2 = slight
Bronch-alv.. = bronchiolo-alveolar
BALT = bronchus-associated lymphoid tissue.
Data obtained from pages 57-58 (MRID 49441803).

Associated with the effects observed in the lung were findings in the tracheobronchial and mediastinal lymph nodes (Table 7). Minimal to slight lympho-reticulocellular hyperplasia in one or both of these lymph nodes was observed in males and females at the mid- and high-exposure concentrations. Hyperplasia was also observed in three females at the low concentration (0 in controls). Macrophage aggregates were observed in the tracheobronchial lymph nodes of 6 males at the mid concentration (minimal to marked numbers), and in 7 males at the high concentration (minimal to marked). Minimal to moderate macrophage aggregates were observed in the tracheobronchial lymph nodes of 8 females at the mid concentration and in 9 females at the high concentration.

TABLE 7. Incidence of lymph node lesions

Tracheobronch. lnn	Male animals				Female animals			
Test group (mg/m³)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)
No. of animals	10	10	10	10	9	10	9	10
Hyperplasia, lympho-reticul.	1	1	0	5	0	3	4	6
• Grade 1	1	1		5		2	4	4
• Grade 2						1		2
Macrophage aggregates	1	1	6	7	0	0	8	9
• Grade 1	1	1	5	2			5	2
• Grade 2			1	2			2	4
• Grade 3				2			1	3
• Grade 4				1				

Mediastinal lnn.	Male animals				Female animals			
Test group (mg/m³)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)	0 (0)	1 (1.4)	2 (7.2)	3 (36.0)
No. of animals	10	10	10	10	10	9	10	10
Hyperplasia, lympho-reticul.	1	0	5	6	0	1	3	4
• Grade 1	1		4	3		1	2	2
• Grade 2			1	3			1	2
Macrophage aggregates	0	0	5	6	0	0	7	8
• Grade 1			3	2			2	3
• Grade 2			1	1			3	4
• Grade 3			1	3			2	1

Grade 1 = minimal; Grade 2 = slight; Grade 3 = moderate; Grade 4 = severe.
Data obtained from pages 58-59 (MRID 49441803).

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The inhalation exposure of rats to Dicamba BAPMA Salt for 28 days caused no substance-related adverse findings regarding clinical signs, body weight, ophthalmology examinations, food consumption, as well as clinical pathology parameters in blood. Histopathology examinations showed morphological changes in the nasal cavity, trachea, larynx, lung, and lung-associated lymph nodes at the mid- and high concentrations, and in some of the respiratory tract tissues at the low concentration. The larynx was the primary tissue affect at the low concentration. A no-observed-adverse-effect-level (NOAEL) for the respiratory tract was not established.

B. REVIEWER COMMENTS:

The Agency agrees with the investigators' conclusion. Microscopic examination of tissues showed that the target organs following inhalation of Dicamba BAPMA Salt were the nasal cavity, larynx, trachea, lungs, and the tracheobronchial and mediastinal lymph nodes. The irritant properties of the test substance were demonstrated by the concentration-dependent increase in the incidences and severity of respiratory tract lesions. The low concentration caused adverse responses such as ulcers in epithelial tissues of the larynx in males, and single/multi-focal hyperplasias in Level I and/or Level II of the larynx in both males and females. The increased mean neutrophil cell counts observed in males from the mid- and high-concentration groups may be a reaction to the respiratory tract lesions, but the finding

was marginal and inconclusive given the lack of response by other differential cell counts (e.g. monocytes).

The LOAEL in Wistar rats was 0.0014 mg/L based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasias in the larynx. A NOAEL was not identified.

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for 4-week inhalation toxicity study in rats (OCSPP 870.3465).

C. STUDY DEFICIENCIES: None.